Remarks

The Office Action dated April 20, 2009 has been carefully reviewed and the following comments are made in response thereto. In view of the following remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicant has amended claims 17 and 26 to recite a recombinant herpes simplex virus in which the γ34.5 gene, the ICP6 gene, and the ICP47 gene have been deleted or inactivated. As a result of this amendment, Applicant changed the dependency of certain claims. In addition, Applicant has introduced claim language and claims that specify that interleukin 18 is administered (a) in an amount so low that the administration of interleukin 18 alone is not effective in treating cancer and (b) at a dose low enough to exhibit no toxicity. Applicant has also introduced a claim directed to the dosage of interleukin-18. Exemplary support for the amendments is found on page 9, line 19 to 21, page 12 line 16 to page 13, line 4 and Examples 1 to 8 (page 18, line 21 to page 27, line 11) of the specification. No new matter has been added.

The Rejections under 35 U.S.C. 112, first paragraph should be withdrawn

Claims 17 to 27 were rejected under 35 U.S.C. 112, first paragraph for (I) allegedly lacking enablement and (II) allegedly failing to comply with the written description requirement.

I. Claims 17 to 27 were rejected for allegedly lacking enablement. Specifically, the Examiner has indicated that the claims are enabled for treating cancer utilizing herpes simplex virus (HSV) wherein the gamma 34.5 gene, ICP6 gene and ICP47 are deleted or inactivated (*see* page 2 of the Office Action). Without acquiescing to the merits of any rejection and for the sole purpose of advancing prosecution, Applicant has amended the pending claims to recite methods of treating cancer utilizing recombinant herpes simplex virus in which the γ34.5 gene, the ICP6 gene and the ICP47 gene have been deleted or inactivated. As amended, the pending claims are clearly enabled (*see* page 2 of the Office Action). Accordingly, this rejection is moot.

II. Claims 17 to 27 were also rejected for rejection for allegedly failing to comply with the written description requirement. Specifically, the Examiner alleges that Applicant only disclosed one HSV vector having a deletion or inactivation in gamma 34.5, ICP6 and ICP47 gene. Furthermore, the Examiner alleges that a written description of the other claimed HSV vectors should be disclosed to overcome this rejection (*see* page 4 of the Office Action). Applicant respectfully disagrees.

As discussed, without acquiescing to the merits of any rejection and for the sole purpose of advancing prosecution, Applicant has amended the pending claims to recite methods of treating cancer utilizing recombinant herpes simplex virus in which the γ34.5 gene, the ICP6 gene and the ICP47 gene have been deleted or inactivated. As amended, these claims clearly comply with the written description requirement.

Based on the disclosure of the specification, those of skill in the art would recognize that the key properties of a recombinant HSV virus according to the present invention are that the γ34.5 gene, the ICP6 gene, and the ICP47 gene have been deleted or inactivated and that the virus is only able proliferate inside cancer cells (*see e.g.* page 8, lines 2 to 25 and page 11, lines 23 to 25). In addition, the specification also discloses a specific example of such a suitable HSV (G47Δ) (*see e.g.* page 9, lines 18 to 22) and that the administration of such a suitable recombinant HSV (*e.g.* G47Δ) is effective for the treatment of cancer. The specification also discloses that the recombinant HSV can be further modified to include interleukin 12 (*see e.g.*, page 11, lines 18 to 25). Given the disclosure, those of skill in the art would recognize that any HSV, having these deletions or inactivations, that selectively replicates in the cancer cells can be used to enhance the effect of oncolytic virus therapy according to the method of the present invention, whether or not the HSV has been further genetically modified, or alternatively, whether or not the HSV can express proteins encoded by the genes useful for anticancer activities (including genes encoding cytokines and interleukins). Accordingly the written description requirement is satisfied and therefore the rejection should be withdrawn (*see* M.P.E.P. 2163 (To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention at the time of application filing)).

The Rejections under 35 U.S.C. 103(a) should be withdrawn

Claims 17 to 27 were as allegedly being obvious over Johnson *et al.* and in view of Hara *et al.* Specifically, the Examiner alleges that it would have been obvious to co-administer both interleukin 12 and interleukin 18 as taught by Hara *et al.* with an expression vector as taught by Johnson *et al.* to induce an enhancing response to against neoplasmia. Applicant respectfully disagrees.

The present invention relates to novel methods of treating cancer which enhance existing oncolytic virus therapy using recombinant HSV, that (a) selectively replicates only within cancer cells, (b) is incapable of replicating in normal cells and (c) does not damage normal tissue (*see* page 1, line 24 to page 2, line 4 of the specification). Oncolytic virus therapy has been and continues to be a promising

treatment for many types of cancer. At the time of the invention, conventional wisdom taught that interleukin 18 inhibits HSV growth and as such interleukin 18 was not used in oncolytic virus therapy. Contrary to that conventional wisdom, Applicant surprisingly discovered that interleukin 18 enhanced the efficacy of oncolytic virus therapy when co-administered with a recombinant HSV that selectively replicates within cancer cells (*see e.g.* page 18, line 21 to page 20, line 3 and page 20, line 21 to page 21, line 20 as well as Figures 1 and 3 of the specification). This surprising discovery is allegedly obvious over the disclosures of Johnson *et al.* and Hara *et al.*

Johnson *et al.* discloses a modified HSV, which may encode a therapeutic product (*e.g.* a cytokine) and which may be used to treat cancer (*see* claims 1 to 5 and claims 33 to 34). However, Johnson *et al.* fails to disclose or suggest any method for enhancing the effect of the oncolytic virus therapy. In particular, Johnson *et al.* fails to disclose or suggest the co-administration of (a) recombinant HSV and (b) interleukin 18. Johnson *et al.* also fails to disclose or suggest the co-administration of (a) recombinant and (b) interleukin 18 and interleukin 12.

The Hara *et al.* article focuses on using the combination of interleukin 12 and interleukin 18 as a cancer vaccine. Hara *et al.* discusses the effectiveness of cancer vaccine therapy using cells transduced with the interleukin 12 gene combined with systemic interleukin 18 administration (*see e.g.* Abstract). Hara *et al.* discovered that the combination of localized interleukin 12 administration and systemic interleukin 18 administration produces a synergistic anti-tumor effect (*see e.g.* Abstract). Hara *et al.* does not disclose or suggest that (a) localized interleukin 12 administration and (b) systemic interleukin 18 administration can be combined with other cancer treatments. Hara *et al.* does not describe or suggest enhancing the effect of oncolytic virus therapy and only emphasizes the synergic anticancer effect by the interaction between interleukin 18 and interleukin 12. Hara *et al.* does not disclose or suggest using a recombinant HSV with interleukin 18 and optionally interleukin 12 to treat cancer.

The combination of the disclosures of Johnson *et al.* and Hara *et al.* clearly does not render the pending claims obvious.

The pending claims are not obvious because the state of the art at the time of the invention taught away from combining interleukin 18 (and optionally interleukin 12) administration with recombinant HSV to treat cancer and failed to provide any motivation to make this combination.

As the Examiner had indicated, the combination of familiar elements according to know methods is likely to be obvious when it does no more than yield predictable results. The combination of the disclosures of Johnson *et al.* and Hara *et al.* is far from predictable. On the contrary, at the time of the

invention, the art taught away from making this combination and fails to provide a motivation to combine.

As disclosed in Fujioka *et al.* (a copy of which was previously submitted), it was well-known at the time of the invention that interleukin 18, when systemically administered, serves to prevent from HSV infection (*see e.g.* page 2402, right column, lines 1 to 22 and page 2407, left column, lines 2 to 10 (HSV infection inhibited)). Accordingly, those of skill in the art would have expected that systemic administration of interleukin 18 would have reduced the effectiveness of the oncolytic virus therapy using recombinant HSV.

At the time of the invention, interleukin 12 was also known to prevent a HSV infection (*see* Matsuo *et al.* (1996) (a copy of which is attached)). Thus, those of skill in the art would have expected that administration of interleukin 12 would reduce the effectiveness of oncolytic virus therapy using recombinant HSV.

Similarly, at the time of the invention, it was known that the combination of interleukin 12 and interleukin 18 are important in the control of HSV virus infection (*see e.g.* Harandi *et al.* (2001) a copy of which is attached). Accordingly, those of skill in the art would have expected that co-administration of interleukin 12 and interleukin 18 would control recombinant HSV infection.

Thus, at the time of the invention, the state of the art taught that interleukin 18, interleukin 12 or their combinations reduce or prevent HSV infection. Accordingly, those of skill in the art would have expected that using those cytokines would negatively impact oncolytic virus therapy, which requires viral proliferation to succeed. At the time of the invention, conventional wisdom in the art taught away from the co-administration of HSV and interleukin 18 (and optionally interleukin 12) and also taught away from achieving the observed enhanced effect on oncolytic virus therapy. Since interleukin 18 and interleukin 12 were known to inhibit HSV replication, those of skill in the art would not have been motivated to combine the disclosures of Johnson *et al.* and Hara *et al.*

None of the references cited disclose or suggest the enhanced oncolytic effect exhibited by co-administration of interleukin 18 and a recombinant HSV virus in which the γ34.5 gene, the ICP6 gene, and the ICP47 gene have been deleted or inactivated or that such an effect can be achieved by administering interleukin 18 at a dose a lower than its therapeutically effective amount.

As mentioned above, Johnson *et al.* discloses that the effects of viral therapy can be augmented if the virus contains a heterologous nucleic acid encoding one or more therapeutic products such as *e.g.* cytokines (*see* page 10, lines 25 to 30). Johnson *et al.* also only discloses the local administration of the therapeutic products encoded by the virus. Furthermore, Johnson *et al.* discloses no actual data for the

effects exhibited by the virus containing the nucleic acid encoding the therapeutic products. Those of skill in the art would understand that when cytokines are used as therapeutic products, they are administered at a therapeutically effective amount to exhibit the desired effect (*e.g.* anti-tumor activity). Those of skill in the art would interpret Johnson *et al.* as disclosing an HSV virus which encodes a therapeutic protein expressed in a therapeutically effective amount.

The claimed methods largely differ from those disclosed by Johnson *et al.* and Hara *et al.* Based on the teachings of those references, it would be very difficult for those of skill in the art to envision co-administration of the herpes virus and interleukin 18 as a protein, even at a low amount which is not the therapeutically effective amount, to obtain the largely or significantly enhanced effect on the oncolytic virus therapy, accompanied by the additional advantage of reduced side effects.

In the claimed methods, interleukin 18 is not used as a therapeutic protein (*i.e.* in therapeutically effective amounts). Rather, interleukin 18 is used a protein enhance to cause the largely or significantly enhanced effect on the oncolytic virus therapy (*i.e.* anti-tumor or tumor-killing effect) exhibited by the herpes simplex virus that selectively replicates in cancer cells such as G47Δ. Optimally and surprisingly, this enhanced effect on oncolytic virus therapy can be obtained even when interleukin 18 is co-administered in an amount low amount so that the administration of interleukin 18 alone is not effective in treating a cancer, as clearly shown in Figures in the present application. Specifically, in the methods of the present invention, even when the amount of interleukin 18 in an amount so low that interleukin 18 alone is not effective to treat cancer, *i.e.* not a "therapeutically effective amount" (*see, e.g.*, the data of "–Mock + IL-18" in Fig. 1, Fig. 2 (B), Fig. 9 (right figure)), the significantly enhanced effects on the oncolytic virus therapy can still be obtained (*see, e.g.*, the data of "G47 delta + IL-18" of Fig. 1, Fig. 2 (B), Fig. 9 (right figure)).

Contrary to the disclosure of the combination of Hara *et al.* and Johnson *et al.*, in the claimed methods, interactions and/or relationships between the recombinant herpes simplex virus and interleukin 18 are critical for the significantly enhanced effects on the oncolytic virus therapy, which does not depend on or results from the interaction between interleukin 18 and interleukin 12 (as shown in Hara *et al.*). Moreover, in the claimed methods, the enhancement effect of interleukin 18 on the oncolytic virus therapy is achieved regardless of whether the recombinant herpes simplex virus carries a gene coding for interleukin 12. Any of concept, approach, and mechanism for the claimed methods is also largely different from those disclosed in Hara *et al.* Thus, it would not be obvious to achieve the methods of the present invention based on the disclosures of Hara *et al.* and Johnson *et al.*

Furthermore, in Johnson *et al.* there is no motivation, suggestion, or teaching to use interleukin-18 alone with recombinant HSV. A viral vector as disclosed in Johnson *et al.* expressing gamma interferon does not achieve the same results as co-administration of interleukin 18 with a recombinant HSV (*compare* page 6 of the Office Action). In addition to gamma interferon, interleukin 18 induces gene expression and synthesis of *e.g.* TNF, IL-1, Fas ligand and several other chemokines (*see* Dinarello (1999) Abstract attached), thus any observed effect by the Applicant might be due to any of the pathways involving interleukin 18. There is a large difference between localized expression of protein carried by a recombinant HSV expressing gamma interferon and the systemic administration of interleukin 18. In particular, it was well-known at the filing of the application that, even when a local administration of the cytokines such as interleukin 18 and interleukin 12 is effective in the anti-tumor effect with little toxic side effect, a systemic administration of the cytokines may cause a serious toxic side effect. Thus, a person skilled in the art would have recognized local administration of interleukin 18 in oncolytic virus therapy does not result in the same effect systemic administration.

In light of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are not obvious over the combination of any of the references cited by the Examiner.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,
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